UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,379	11/22/2005	James M. Swanson	51674/CAB/R2682	6018

23363 7590 08/14/2007
CHRISTIE, PARKER & HALE, LLP
PO BOX 7068
PASADENA, CA 91109-7068

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
08/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,379	SWANSON ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed May 22, 2007. Currently, claims 1-8 are pending. Claims 7-8 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Election/Restrictions

4. Applicant's election without traverse of Group 1, Claims 1-6 in the paper filed May 22, 2007 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Priority

5. This application claims priority to provisional application 60/433,045, filed December 13, 2002.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

The instant provisional application has not been referred to in the Ads sheet or the first line of the specification.

Drawings

6. The drawings are unacceptable.

Figures 1 and 2 and 3 refer to colors which are not depicted in the instant figures. No color drawings are presented.

Figure 2 contains sequences which are not identified by SEQ ID NO:.

Sequence Rules

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

a. The drawings contain sequences which are not identified by SEQ ID NO:.

b. The specification provides sequences on page 6 which are not identified by SEQ ID NO:.

Information Disclosure Statement

8. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office; and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate

paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

c. Pages 15-17, 25-28 are not information disclosure statements.

9. The information disclosure statement filed 3/20/06 fails to completely comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because two references do not contain a date for publication and thus have been lined through. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA…' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. As provided in Example 11 of the Written Description Guidelines, no common structural attributes identify the members of the genus of "a marker within a block of linkage disequilibrium surrounding the DRD4 7R allele". The current claims encompass a large genus of nucleic acids which comprise variants in any region of any a marker within a block of linkage disequilibrium surrounding the DRD4

7R allele. The genus includes an enormous number of variants, polymorphisms and mutations for which no written description is provided in the specification. This large genus is represented in the specification by only a single named polymorphism for which data is provided, namely the repeat polymorphism in exon 3, DRD4-7R. This genus encompasses SNPs, deletions, insertions, translocations, microsatellites, for example.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a marker within a block of linkage disequilibrium surrounding the DRD4 7R allele alone is insufficient to describe the genus. There is no description of the mutational sites that exist in nature. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. The polymorphisms shown are not representative of the genus of any a marker within a block of linkage disequilibrium surrounding the DRD4 7R allele because it is not clear which polymorphisms within the gene (coding or non-coding) region of DRD4 nucleic acid would have the same effect. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is

insufficient to support the claim. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method of testing a patient for ADHD by testing for a marker within a block of linkage disequilibrium surrounding the DRD4 7R allele and evaluating the level of dopamine release.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches girls and boys respond differently to the effects of exercise on children with ADHD. Tantillo et al. (Medicine and Science in Sports & Exercise, 2002, pages 203-212). Tantillo teaches that the boys and girls had different reactions to exercise with ADHD. The findings suggest an interaction between sex and exercise intensity that is not explained by physical fitness. Thus, it is unpredictable that girls and boys experience the same levels and response to stimulus.

The post filing date art analyzes the connection between yoga, and ADHD ("The effects of Yoga on ADHD" Kelley Martin, Lamar University). Martin teaches that the study presented did not support the hypothesis. Results displayed no significant difference between the treatment and non-treatment groups on both the attention problems and the hyperactivity scales (page 14). Thus, it appears that not all stimulus are statistically associated with treatment and non-treatment groups.

Finally, the art teaches dogs are affected by ADHD. Vas et al. (Applied Animal Behavior Science, Vol 103, pages 105-117, 2007). Vas applies the application and validation questionnaire from humans to dogs.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002)

teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the

gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that the full scope of the claimed invention may be practiced as broadly as claimed. The specification teaches analysis of 10 male subjects (8 Caucasian and two Hispanics). As illustrates in Figure 6, the level of dopamine is statistically different only in response to exercise at the peak time following the baseline measurement. At 30 minutes and 60 minutes the differences is not significant. Moreover, there is no indication of the 7R allele status of the various patients. There is not stratification of those ADHD patients with and without the 7R allele or those controls with the 7R allele. Thus, it is unclear how the 7R allele factors into the analysis. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied

The claims are broadly drawn to any patient. A patient would encompass any animal, including dogs and cats. Moreover, the claims would encompass any ethnicity, any sex and adults and children. The art teaches that a study of children illustrated that girls and boys had different response to exercise (see Tantillo). Thus, within the subpopulation of children, boys and girls had different responses to exercise. The instant specification teaches the use of only boys. It is unpredictable whether girls would show the same responses. The instant specification samples boys from age 7-11

(see table 2). The specification further teaches that the alleles of the 7R varies between ethnic groups. Moreover, at the time the invention was made, there was not contemplation of dogs, cats, for example within the scope of patient. Vas teaches that dogs may suffer from ADHD and benefit from questionnaires and validation. However, at the time the invention was made, the art fails to provide any guidance of the 7R or dopamine levels of canines for testing a dog for ADHD. The skilled artisan would be required to perform trial and error experimentation to practice the broad scope of the instant claims. The claims encompass any patient, human, dog, children, adults, of any sex and ethnicity. The art teaches the unpredictability between these subgroups. Thus, it would constitute undue, unpredictable experimentation to practice the broad scope of the claims without further trial and error experimentation.

The claims are drawn to a method of testing for the presence of a marker within a block of linkage disequilibrium surrounding the DRD4 7R allele. The specification teaches a single DRD4 7R allele. The specification fails to provide any guidance of additional markers. It would require unpredictable trial and error experimentation to determine which alleles identified are in linkage disequilibrium and surrounding the 7R allele. The art, namely Meyer, teaches SNPs within the same gene, in the same block are not associated with the same diseases. Thus, the skilled artisan would be unable to assume that any SNPs or variant located in proximity to the 7R alleles would be in linkage disequilibrium and encompassed within the scope of the claims.

The claims are drawn to evaluating "the level of dopamine" but fails to provide any context of level of dopamine. The specification illustrates levels on a scale of 5-25, but fails to provide any guidance which levels are indicative of ADHD and normal individuals. Inter-individual variation would be expected. Moreover, the specification illustrates that the only statistically significant difference occurred at peak exercise and

not at 30 or 60 minutes following exercise. Thus, the evaluation of dopamine levels would have been unpredictable at the points after peak evaluation. Moreover, there is no indication of the 7R allele status of the various patients. There is not stratification of those ADHD patients with and without the 7R allele or those controls with the 7R allele. Thus, it is unclear how the 7R allele factors into the analysis.

The claims are drawn to any stimulus. A stimulus would broadly encompass any pin prick, fireworks, music, drug administration, yoga or smoking, for example. The specification teaches analyzing for the stimulus of exercise for dopamine levels. The art teaches that yoga is not statistically different between ADHD and non-treatment individuals. While the skilled artisan could perform further experimentation to determine whether an individual has ADHD by testing any number of stimuli including exercise, drug administration, yoga or smoking, the results of the experimentation are unpredictable. The trial and error experimentation would amount to inventive analysis because the results of such experimentation is unpredictable given the teachings in the art.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the claims broadly encompass subject matter that is not enabled in the art and specification.

Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of associating alleles with phenotypes without further unpredictable and undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-6 are indefinite because it is unclear whether the claims are drawn to a method of testing a patient for ADHD or whether the method is for evaluating the level of dopamine release in response to a stimulus. The preamble fails to provide any connection to the final process of the method to provide the ordinary artisan any guidance as to testing a patient for ADHD. It is unclear how evaluating the level of dopamine release in response to a stimulus indicates a test for ADHD and how the

ordinary artisan would provide an analysis of ADHD. It is unclear whether the method is directed to testing a patient for ADHD or whether the method is for evaluating the level of dopamine release in a patient in response to a stimulus.

B) Claim 6 is directed to a method where the marker corresponds to the DRD4 7R allele. It is unclear what "corresponds to" encompasses. It is unclear whether the claims are limited to the DRD4 7R allele or whether "corresponds" is broader in scope and if so, how much broader in scope and to what extend.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 1-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Wigal et al. (Pediatric Research, Vol. 53, No. 5, pages 756-761, May 2003).

It is noted that the authorship of the Wigal et al. reference is distinct from the inventorship of the instant application and that this rejection may be overcome by the filing of a 132 Katz-type declaration.

Given that the priority claim to the provisional application is not perfected, the following 102(a) rejection is appropriate.

Wigel teaches catecholamine response to exercise in children with ADHD. Wigal teaches the same analysis provided in the instant specification. Wigal teaches that CA

excretion after exercise challenges in children with ADHD is deficient and that the deficiency can be detected using minimally invasive nonpharmacologic challenge (abstract). Wigel teaches that circulating DA increased significantly in the control subjects, but no increase was noted in the subjects with ADHD. Wigel thus teaches as much as the instant specification.

Conclusion

14. No claims allowable.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

Jeanine Goldberg
Primary Examiner
August 2, 2007